

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants: Klaus Michael Debatin et al.  
Title: Smac-peptides as Therapeutics against Cancer  
and Autoimmune Diseases  
Appl. No.: 10/511,037  
Filing Date: 01/19/2005  
Examiner: Unassigned  
Art Unit: Unassigned

**INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 CFR §1.56**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56.

A copy of each non-U.S. patent document and each non-patent document is being submitted to comply with the provisions of 37 CFR §1.97 and §1.98, except as noted below.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* art reference against the claims of the present application.

**TIMING OF THE DISCLOSURE**

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

**RELEVANCE OF EACH DOCUMENT**

Documents A1- A27 were cited as being relevant during the prosecution of the corresponding International application. Copies of the documents are not being provided since copies should have been provided directly by WIPO under an exchange program between the PTO, the EPO and the JPO. A copy of the International Search Report setting forth the portion of each reference considered relevant by the examiner is attached.

The relevance of Documents A28 and A29 is explained in the specification.

Applicants respectfully request that any listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 CFR §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

Date Jan 19, 2005

By Michele M. Simkin

FOLEY & LARDNER LLP  
Customer Number: 22428  
Telephone: (202) 672-5538  
Facsimile: (202) 672-5399

Michele M. Simkin  
Attorney for Applicants  
Registration No. 34,717

Under the Paperwork Reduction Act of 1995, no responses are required to respond to a collection of information unless it contains a valid OMB control number.

|  |   |    |   |                          |                       |
|--|---|----|---|--------------------------|-----------------------|
| Substitute for form 1449B/PTO<br><b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b><br><br>(use as many sheets as necessary) |   |    |   | <b>Complete if Known</b> |                       |
|  |   |    |   | Application Number       | 10/511,037            |
|  |   |    |   | Filing Date              | 01/19/2005            |
|  |   |    |   | First Named Inventor     | Klaus Michael Debatin |
|  |   |    |   | Group Art Unit           | Unassigned            |
|  |   |    |   | Examiner Name            | Unassigned            |
| Sheet  | 1 | of | 3 | Attorney Docket Number   | 085449-0152           |

## U.S. PATENT DOCUMENTS

| Examiner Initials* | Cite No. <sup>1</sup> | U.S. Patent Document |                                   | Name of Patentee or Applicant of Cited Document | Date of Publication of Cited Document MM-DD-YYYY | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
|--------------------|-----------------------|----------------------|-----------------------------------|---|--|---|
|                    |                       | Number               | Kind Code <sup>2</sup> (if known) |   |  |   |
|                    | A1                    | 6,306,613            | B1                                | BAIRD ET AL.                                    | 10/23/2001                                       |   |
|                    |                       |                      |                                   |   |  |   |
|                    |                       |                      |                                   |   |  |   |
|                    |                       |                      |                                   |   |  |   |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No. <sup>1</sup> | Foreign Patent Document |                     |                                   | Name of Patentee or Applicant of Cited Documents | Date of Publication of Cited Document MM-DD-YYYY | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T <sup>6</sup> |
|--------------------|-----------------------|-------------------------|---------------------|-----------------------------------|--|--|---|----------------|
|                    |                       | Office <sup>3</sup>     | Number <sup>4</sup> | Kind Code <sup>5</sup> (if known) |  |  |   |                |
|                    | A2                    | WO                      | 02/16418            | A                                 | THOMAS JEFFERSON UNIVERSITY                      | 02/28/2002                                       |   |                |
|                    | A3                    | WO                      | 02/16402            | A                                 | BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM | 02/28/2002                                       |   |                |
|                    | A4                    | WO                      | 02/26775            | A                                 | TRUSTEES OF PRINCETON UNIVERSITY                 | 04/04/2002                                       |   |                |
|                    | A5                    | WO                      | 01/49719            | A                                 | UNIVERSITY OF TEXAS SYSTEM                       | 07/12/2001                                       |   |                |
|                    | A6                    | WO                      | 00/58488            | A                                 | INVITROGEN CORP.                                 | 10/05/2000                                       |   |                |
|                    | A7                    | WO                      | 01/38547            | A                                 | ROSENECKER ET AL.                                | 05/31/2001                                       |   |                |
|                    | A8                    | WO                      | 00/29427            | A                                 | CYCLACEL LTD.                                    | 05/25/2000                                       |   |                |
|                    | A9                    | WO                      | 99/05302            | A                                 | PERKIN ELMER CORP.                               | 02/04/1999                                       |   |                |
|                    | A10                   | EP                      | 0 903 408           | A                                 | BIOGEN INC.                                      | 03/24/1999                                       |   |                |
|                    | A11                   | WO                      | 94/04686            | A                                 | BIOGEN INC.                                      | 03/03/1994                                       |   |                |
|                    |                       |                         |                     |                                   |  |  |   |                |
|                    |                       |                         |                     |                                   |  |  |   |                |
|                    |                       |                         |                     |                                   |  |  |   |                |

## NON PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. <sup>1</sup> | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.   | T <sup>6</sup> |
|--------------------|-----------------------|--|----------------|
|                    | A12                   | ENDO ET AL., "Cysteine, basic and neutral amino acid transporter BAT1 from rat an human activated by rBAT, cDNA, and recombinant expression," DATABASE CA 'Online!, CHEMICAL ABSTRACTS SERVICE, Columbus, Ohio, US; 2001, XP002204777, retrieved from STN, Database accession no. 134:174559 HCA abstract & JP 2001 046070 A (FOUNDATION FRO SCIENTIFIC TECHNOLOGY PROMOTION, JAPAN) 20 February 2001. |                |
|                    | A13                   | DEROSSI ET AL., "Trojan Peptides: The Penetratin System for Intracellular Delivery," TRENDS IN CELL BIOLOGY, Elsevier Science Ltd., vol. 8, February 1998, pp. 84-87, XP002940006, ISSN: 0962-924.   |                |

|                    |                 |
|--------------------|-----------------|
| Examiner Signature | Date Considered |
|--------------------|-----------------|

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

<sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Under the Paperwork Reduction Act of 1995, no responses are required to respond to a collection of information unless it contains a valid OMB control number.

|  |   |    |   |                               |                       |
|--|---|----|---|-------------------------------|-----------------------|
| Substitute for form 1449B/PTO                            |   |    |   | <b>Complete if Known</b>      |                       |
| <b>INFORMATION DISCLOSURE<br/>STATEMENT BY APPLICANT</b> |   |    |   | <b>Application Number</b>     | 10/511,037            |
|  |   |    |   | <b>Filing Date</b>            | 01/19/2005            |
|  |   |    |   | <b>First Named Inventor</b>   | Klaus Michael Debatin |
|  |   |    |   | <b>Group Art Unit</b>         | Unassigned            |
|  |   |    |   | <b>Examiner Name</b>          | Unassigned            |
| (use as many sheets as necessary)                        |   |    |   | <b>Attorney Docket Number</b> | 085449-0152           |
| <b>Sheet</b>   | 2 | of | 3 |                               |                       |

**NON PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No. <sup>1</sup> | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.   | T <sup>6</sup> |
|--------------------|-----------------------|--|----------------|
|                    | A14                   | SCHWARZE ET AL., "In vivo protein transduction: delivery of a biologically active protein into the mouse," SCIENCE, American Association for the Advancement of Science, vol. 285, no. 5433, 3 September 1999, pp. 1569-1572, XP002140133, ISSN: 0036-8075.  |                |
|                    | A15                   | FISCHER ET AL., "Structure-Activity Relationship of Truncated and Substituted Analogues of the Intracellular Delivery Vector Penetratin," JOURNAL OF PEPTIDE RESEARCH, Munksgaard International Publishers, vol. 55, no. 2, February 2000, pp. 163-172, XP000899124, ISSN: 1397-002X.                          |                |
|                    | A16                   | FULDA ET AL., "Release of Smac from mitochondria bypasses the Bcl-2 inhibition in type II cells and sensitizes for death receptor or drug-induced apoptosis," PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 42, March 2001, p. 552, XP002251122, ISSN: 0197-016X, abstract. |                |
|                    | A17                   | FULDA ET AL., "Smac release from mitochondria bypasses the Bcl-2 inhibition and sensitizes tumor cells for death receptor or drug-induced apoptosis," BLOOD, November 16, 2001, vol. 98, no. 11, Part 1, pp. 572a-573a, XP002251123, ISSN: 0006-4971, abstract.  |                |
|                    | A18                   | FULDA ET AL., "Smac peptides or Smac gene transfer as a novel strategy to overcome resistance against TRAIL- or drug-induced apoptosis," PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 43, March 2002, pp. 527-528, XP002251124, ISSN: 0197-016X, abstract.                 |                |
|                    | A19                   | JOHNSTONE ET AL., "Apoptosis: A link between cancer genetics and chemotherapy," CELL, vol. 108, no. 2, 25 January 2002, pp. 153-164, XP002251125, ISSN: 0092-8674.   |                |
|                    | A20                   | IGNEY ET AL., "Death and anti-death: Tumour resistance to apoptosis," NATURE REVIEWS CANCER, vol. 2, no. 4, 20 April 2002, pp. 277-288, XP002251126, ISSN: 1474-175X.  |                |
|                    | A21                   | FULDA ET AL., "Smac agonists sensitize for Apo2L/TRAIL- or anticancer drug-induced apoptosis and induce regression of malignant glioma in vivo," NATURE MEDICINE, vol. 8, no. 8, August 2002, pp. 808-815, XP002251127, ISSN: 1078-8956, abstract.   |                |
|                    | A22                   | SILKE ET AL., "The anti-apoptotic activity of XIAP is retained upon mutation of both the caspase 3- and caspase 9-interacting sites," JOURNAL OF CELL BIOLOGY, vol. 157, no. 1, 1 April 2002, pp. 115-124, XP002272040, ISSN: 0021-9525, abstract.   |                |
|                    | A23                   | EKERT ET AL., "DIABLO promotes apoptosis by removing MIHA/XIAP from processed caspase 9," JOURNAL OF CELL BIOLOGY, vol. 153, no. 3, 30 April 30, 2001, pp. 483-490, XP002272041, ISSN: 0021-9525, abstract.  |                |
|                    | A24                   | SRINIVASULA ET AL., "A conserved XIAP-interaction motif in caspase-9 and Smac/DIABLO regulates caspase activity and apoptosis," NATURE, vol. 410, 1 March 2001, pp. 112-116, XP002962286, ISSN: 0028-0836.   |                |
|                    | A25                   | VERHAGEN ET AL., "HtrA2 promotes cell death through its serine protease activity and its ability to antagonize inhibitor of apoptosis proteins," JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 1, 4 January 2002, pp. 445-454, XP002957689, ISSN: 0021-9258.  |                |
|                    | A26                   | HOLCIK ET AL., "Translation Upregulation of X-Linked Inhibitor of Apoptosis (XIAP) Increases Resistance to Radiation Induced Cell Death," ONCOGENE, vol. 19, no. 36, 24 August 2000, pp. 4174-4177, XP008007068, ISSN: 0950-9232.  |                |

Examiner  
Signature

Date  
Considered

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

<sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Under the Paperwork Reduction Act of 1995, no responses are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449B/PTO  
**INFORMATION DISCLOSURE  
 STATEMENT BY APPLICANT**

(use as many sheets as necessary)

Sheet 3 of 3

**Complete if Known**

|                        |                       |
|------------------------|-----------------------|
| Application Number     | 10/511,037            |
| Filing Date            | 01/19/2005            |
| First Named Inventor   | Klaus Michael Debatin |
| Group Art Unit         | Unassigned            |
| Examiner Name          | Unassigned            |
| Attorney Docket Number | 085449-0152           |

**NON PATENT LITERATURE DOCUMENTS**

| Examiner Initials* | Cite No. <sup>1</sup> | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published. | T <sup>6</sup> |
|--------------------|-----------------------|--|----------------|
|                    | A27                   | VERHAGEN ET AL., "Identification of DIABLO, a mammalian protein that promotes apoptosis by binding to an antagonizing IAP proteins," CELL, vol. 102, no. 1, 7 July 2000, pp. 43-53, XP002175397, ISSN: 0092-8674.  |                |
|                    | A28                   | DU ET AL., "Smac, a Mitochondrial Protein that Promotes Cytochrome c-Dependent Caspase Activation by Eliminating IAP Inhibition," CELL, vol. 102, pp. 33-42, July 7, 2000.   |                |
|                    | A29                   | CARSON ET AL., "Smac is Required for Cytochrome c-induced Apoptosis in Prostate Cancer LNCaP Cells <sup>1</sup> ," CANCER RESEARCH, vol. 62, pp. 18-23, January 1, 2002.   |                |
|                    |                       |  |                |
|                    |                       |  |                |
|                    |                       |  |                |

Examiner  
Signature

Date  
Considered

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Unique citation designation number. <sup>2</sup> See attached Kinds of U.S. Patent Documents. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

<sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

Burden Hour Statement: This form is estimated to take 2.0 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.